REMARKS

Claims 1-23 and 43-53 are pending and under examination. Applicants have hereinabove canceled claims 3, 8, 18-19, and 48-53, without prejudice. Applicants have also amended claims 13, 17, and 23. Claims 13 and 17 have been rewritten as Markush claims to insert "are/is selected from the group consisting of", to delete the "or" and insert "and" between the last two species and raise no issue of new matter. Support for the amendment of claim 23 may be found in the specification inter alia at page 36, lines 8-9 and the amendment raises no issue of new matter. Accordingly, applicants respectfully request that the Examiner enter the Amendment. Upon entry of the Amendment, claims 1, 2, 4-7, 9-17, 20-23, ans 43-47, as amended, will be pending and under examination in the subject application.

RESTRICTION REQUIREMENT

The Examiner stated that applicant's election with traverse of species microcapsule, endocrine cells that produce insulin, and cells that are not genetically engineered in Paper No. 6 is acknowledged. The Examiner stated that the traversal is on the ground(s) that a search directed to the independent claim would uncover any art relating to the alleged species. The Examiner stated that this is not found persuasive because the searches for the species are not co-extensive, restriction for examination purposes as indicated is proper.

The Examiner stated that the requirement is still deemed proper and is therefore made final.

The Examiner stated that accordingly, claims 1, 2, 4-7, 9-17, 20-

23, 43-47, species microcapsule, endocrine cells that produce insulin, and cells that are not genetically engineered are under examination. The Examiner stated that claims 3, 8, 18-19, 48-53 are not examined because they are drawn to non-elected claims, i.e. claim 3, drawn to a hollow fiber, a disc or a sphere; claim 8, drawn to transplanted genetically engineered cells; claims 18-19, drawn to neuroectodermal cells; and claims 48-53, drawn to a method of inhibiting graft rejection, using a substance, CTLA4Ig, which inhibits the immune-system costimulation, without altering the cytokine profile of the subject, i.e. via encapsulated engineered cells that produce CTLA4Ig.

In response, applicants maintain the previous election of species of (A) endocrine cells which (B) are insulin producing cells and (C) cells that are not genetically engineered cells, with traverse. Applicants have hereinabove canceled non-elected claims without prejudice to applicants' right to pursue the subject matter of these claims at a later date.

Applicants have also canceled without prejudice claims 3, 8, 18-19, and 48-53, which are non-elected.

CLAIM OBJECTION

The Examiner objected to claims 13 and 17 are because claims 13 and 17 are Markush claims, which are not properly written.

In response applicants have amended claims 13 and 17 as Markush claims to insert "are/is selected from the group consisting of", to delete the "or" and insert "and" between the last two species.

Applicants maintain that the amendment of claims 13 and 17 obviates the Examiner's objection and respectfully request that the Examiner reconsider and withdraw the objection to claims 13 and 17.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner rejected claim 23 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that claim 23 is indefinite because it is not clear whether the language ...inhibiting...activated macrophages "capable of "reacting with the viable cells...means...inhibiting...macrophages "from "reacting with the viable cells... or ...inhibiting the activation of macrophages, which is capable of reacting with the viable cells.

In response, applicants have amended claim 23 to recite: "The method of claim 1, wherein inhibiting the subject's immune system from responding to said contained cells or tissue comprises inhibiting production of immunoglobulins and inhibiting activation of macrophages capable of reacting with the viable cells or tissue."

Applicants maintain that the amendment of claim 23 obviates the Examiner's rejection and respectfully request that the Examiner reconsider and withdraw the rejection of claims 23.

REJECTION UNDER 35 U.S.C. §103

The Examiner rejected claims 1, 2, 4-7, 9-17, 20-23, 43-47 under 35

U.S.C. §103(a) as being unpatentable over Lenschow, DJ et al., 1992, Science, 257:789-792, in view of Goosen et al, PN=4,673,566, Soon-Shiong P et al., 1990, Horm Metab Res Suppl, 25: 215-9, Akalin, E et al., 1996, Transplantation, 62(12):1942-5, Linsley, PS, et al., 1994, EP 0 613 944, Padrid PA et al., 1998, Am J Respir Cell Mol Biol, 18(4):453-62, Steurer, W et al., 1995, J. Immunol, 155(3):1165-74.

The Examiner stated that claims 1, 2, 4-7, 9-17, 20-23, and 43-47 are drawn to a method for preventing graft rejection of transplanted insulin-producing cells, by 1) prior to transplantation, containing grafted cells in a microcapsule, and 2) administering soluble CTLA4Ig, which inhibits the production of immunoglobulins, and the activation of macrophages, and which increases the production of gamma-interferon and binds to complement. The Examiner stated that the microcapsule is impermeable to immunoglobulin and/or lymphocytes.

The Examiner stated that Lenschow et al. teach CTLA4Ig blocks human pancreatic islet rejection in mice by affecting T cell recognition of B7+antigen-presenting cells.

The Examiner stated that Lenschow et al. do not teach encapsulation of transplanted cells in a microcapsule which is impermeable to immunoglobulin and/or lymphocytes. The Examiner stated that Lenschow et al. do not teach that CTLA4Ig inhibits the production of immunoglobulins, and the activation of macrophages, and that CTLA4Ig increases the production of gamma-interferon and binds to complement.

The Examiner stated that Goosen et al. teach microencapsulation of transplanted islets of Langerhans in a semipermeable microcapsule, which is impermeable to immune system proteins. The Examiner stated that said microcapsule has a molecular weight cut of below about 150,000 Dalton, and has a controlled thickness of polylysine.

The Examiner stated that Soon-Shiong et al. teach that microencapsulation of isolated islets prevents graft rejection, by protecting the transplanted cells from both cytotoxic T-lymphocytes and natural killer cells.

The Examiner stated that Akalin et al. teach that CTLA4Ig inhibits cell-mediated and humoral immune response, and prevents macrophage activation and infiltration into the graft site.

The Examiner stated that Linsley et al. teach that CTLA4Ig inhibits immunoglobulin secretion (p.19).

The Examiner stated that Padrid et al. teach that interferon-gamma in CTLA4Ig-treated mice increases significantly as compared to the untreated animal.

The Examiner stated that Steurer et al. teach that because of the mutation in the C'1q binding sites of the Fc portion of CTLA4Ig, CTLA4Ig binds to, but does not target, cells for complement-directed cytolysis (abstract).

The Examiner stated that the art establishes that it was possible at the time the invention was made to block human pancreatic islet

rejection in mice using CTLA4Ig, which affects T cell recognition of B7+ antigen-presenting cells. The Examiner stated that the art further teaches that graft rejection of transplanted islet cells could be prevented by microencapsulation of islet cells, wherein by a molecular weight cut off at about 150,000 Dalton, the semipermeable membrane does not allow cytotoxic T-lymphocytes and natural killer cells to reach the grafted cells, thus preventing the graft rejection. The Examiner stated that the art also teaches that CTLA4Ig inhibits the production of immunoglobulins, and the activation of macrophages, and that CTLA4Ig increases the production of gamma-interferon and binds to complement.

The Examiner stated that therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to block human pancreatic islet rejection in mice using CTLA4Ig, which affects T cell recognition of B7+ antigen-presenting cells, as taught by Lenschow et al. The Examiner stated that it would have been obvious to encapsulate the grafted cells, which are (sic) treated with CTLA4Ig, as taught by Goosen et al. and Soon-Shiong et al., because the encapsulation also prevents graft rejection, but by a different mechanism, thus by logical reasoning, would increase the chance of preventing graft rejection by the immune system. The Examiner stated that it would have been obvious to use microcapsules that are impermeable to cytotoxic T-lymphocytes and natural killer cells to reach the grafted cells, for preventing the graft rejection by said immune-system, as taught by Goosen et al. and Soon-Shiong et al. The Examiner stated that the one of ordinary skill in the art would have been expected that CTLA4Ig inhibits the production of

immunoglobulins, and the activation of macrophages, and that CTLA4Ig increases the production of gamma-interferon and binds to complement, because they are inherent properties of CTLA4Ig, as taught by Akalin et al., Linsley et al., Padrid et al., and Steurer et al. The Examiner stated that one of ordinary skill in the art would have been motivated to block encapsulated pancreatic islet rejection using CTLA4Ig, with a reasonable expectation of success. The Examiner stated that the motivation is obvious, i.e. to prevent graft rejection of islet cells.

In response, applicants respectfully traverse the Examiner's rejection of claims 1, 2, 4-7, 9-17, 20-23, and 43-47 under 35 U.S.C. 103(a) and maintain that claims 1, 2, 4-7, 9-17, 20-23, and 43-47 are not obvious over Lenschow, D.J. et al., in view of Goosen et al., Soon-Shiong P. et al., Akalin, E. et al., Linsley, P.S., et al. - EP 0 613 944, Padrid P.A. et al., and Steurer, W. et al.

Applicants maintain that Lenschow, DJ et al., when combined with Goosen et al., Soon-Shiong P et al., Akalin, E et al., Linsley, PS, et al. - EP 0 613 944, Padrid PA et al., and Steurer, W et al. do **not** teach or suggest the claimed method of inhibiting viable cells transplanted into a subject from being destroyed by the subject's immune system which comprises: a) containing the viable cells, or tissue comprising the viable cells, prior to transplantation within a device comprising a semipermeable membrane; **and** b) treating the subject with a substance which inhibits an immune-system costimulation event in an amount effective to inhibit the subject's immune system from responding to said contained cells or tissue, as recited in claim 1. (Emphasis added)

Further in response, to establish a prima facie case of obviousness, three criteria must be met: First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; second, there must be a reasonable expectation of success; and finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. see M.P.E.P. 2143. Moreover, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. M.P.E.P. 2143 citing In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Lenschow et al., as stated on page 789, attempted to develop a treatment that affected only the transplant antigen-specific T cells, thus inducing donor-specific tolerance. The effects of blocking the CD28-B7 interaction in vivo were examined by eliminating mouse pancreatic islet β cell function by treatment with streptozotocin, grafting human pancreatic islets under the kidney capsule and treating with CTLA4Ig after surgery. (See page 790, column 1) Islet rejection was delayed in animals treated with CTLA4Ig compared to the controls with three of seven animals maintaining normal glucose levels for over 80 days. Upon increasing the dosage of CTLA4Ig 100% of the animals maintained normal islet function with no signs of rejection crisis. (See page 790, column 2) In conclusion at page 792, Lenschow et al. state that "the capacity of CTLA4Ig to significantly prolong human islet graft survival in mice in a donor-specific manner suggests that blocking

the interaction of costimulatory molecules such as CD28-B7 may provide an approach to immunosuppression." (emphasis added)

Thus, there is no teaching or suggestion by Lenschow et al. to 1) contain grafted cells in a microcapsule **prior to** transplantation, i.e. no other approach to inhibit viable cells transplanted into a subject from being destroyed by the subject's immune system in conjunction with administration of CTLA4Ig is disclosed by Lenschow et al. Lenschow et al. do not provide any motivation to combine their treatment method that affects only the transplant antigen-specific T cells to induce donor-specific tolerance with other references to arrive at the claimed method which comprises **both** a) containing the viable cells, or tissue comprising the viable cells, **prior** to transplantation within a device comprising a semipermeable membrane; **and** b) treating the subject with a substance which inhibits an immune-system costimulation event in an amount effective to inhibit the subject's immune system from responding to said contained cells or tissue, as recited in claim 1.

Goosen et al. disclose microencapsulation of living tissue or cells for implantation in the body for long term treatment of diabetes or other disease requiring organ transplantation. The microcapsules are biocompatible semi-permeable membranes having a biocompatible negatively charged surface. (see column 3, lines 13-18 and column 7, lines 50-54) Goosen et al. provide examples of microencapsulation of islets of Langerhans and viability thereof (Examples 1 and 2); injection of microencapsulated islets into diabetic rats wherein the islets survived up to 52 weeks (Example

3); multiple injections of microencapsulated islets, wherein two injections allowed control of blood sugar for longer than six months and five injections controlled the level of blood sugar for three months (Example 4); the injection of microencapsulated rat islets into diabetic mice which demonstrates cross-species transplants surviving for over two months (Example 5); the viability of recovered microencapsulated transplanted islets (Example 6); the use of polyvinyl alcohol and polyacetic acid as the external surface of microcapsules (Examples 8 and 9); preparation of spherical calcium alginate droplets using the critical parameters and parameters outside the critical range (Examples 10 and 11); and increasing the strength of the microcapsules with glutaraldehyde (Example 12).

However, Goosen et al. do **not** disclose that treatment comprising microencapsulation of tissue or cells for implantation may be combined with treating the subject with a substance which inhibits an immune-system costimulation event in an amount effective to inhibit the subject's immune system from responding to said contained cells or tissue, as disclosed in step (b) of claim 1 of the subject invention. Goosen et al. do not suggest combination of their microencapsulation method with any other treatment or specifically the teaching of Lenschow et al., i.e. also administering CTLA4Ig. Goosen et al. do not provide any motivation to combine their treatment method with other references to arrive at the claimed method which comprises **both** a) containing the viable cells, or tissue comprising the viable cells, **prior** to transplantation within a device comprising a semipermeable membrane; **and** b) treating the subject with a substance which

inhibits an immune-system costimulation event in an amount effective to inhibit the subject's immune system from responding to said contained cells or tissue. Accordingly, there is no suggestion that an increase in prevention of graft rejection would result when combining encapsulation with CTLA4Ig treatment. Without more, there is no reasonable expectation that combining Lenschow et al. with Goosen et al. will result in success. Therefore, claims 1, 2, 4-7, 9-17, 20-23, and 43-47 are not obvious over Lenschow, DJ et al., in view of Goosen et al.

As discussed below, the addition of Soon-Shiong P. et al., Akalin, E. et al., Linsley, P.S., Padrid P.A. et al., and Steurer, W. et al. to the combination of Lenschow, D.J. et al. and Goosen et al., as discussed above, do not cure the failure of Lenschow, DJ et al. and Goosen et al. to suggest a combination of references to arrive at the claimed method.

Soon-Shiong P. et al., disclose that microencapsulation with a biocompatible semi-permeable capsule membrane prevents specific cytotoxic T-lymphocyte (CTL) and nonspecific natural killer (NK) cell-mediated cytotoxicity. In the discussion at page 217 through page 218, line 2, Soon-Shiong P. et al. state that microencapsulation has the potential not only to allow transplantation in early diabetes <u>without immunosuppressive therapy</u>, but also might allow the use of xenografts to overcome the donor pancreas supply problem. Accordingly, Soon-Shiong P. et al. do not envision combining microencapsulation with any immunosuppressive drug, which would **not** provide one of skill in the art with the suggestion to combine the teachings, nor any

reasonable expectation of success thereof, to treat the subject with a substance which inhibits an immune-system costimulation event in an amount effective to inhibit the subject's immune system from responding to said contained cells or tissue as set forth in step (b) of claim 1, **in combination with** containing the viable cells, or tissue comprising the viable cells, prior to transplantation within a device comprising a semipermeable membrane, as recited in step (a) of claim 1. Therefore, Soon-Shiong P. et al. do not motivate one of skill to combine the teachings of Lenschow, DJ et al. and Goosen et al. to arrive at the claimed method.

Akalin, E. et al., demonstrate that inhibition of Th1 cell function by CTLA4Ig is associated with inhibition of cell-mediated and humoral immune responses in vivo, including downregulation of expression of macrophage activation and growth factor expression in the target organ and suggest targeting t-cell costimulation as a new approach to prevent chronic allograft rejection. Akalin et al. do not disclose microencapsulation of tissue or cells prior to renal transplantation, as recited in step (a) of claim 1 to be used in combination with CTLA4Ig administration. Accordingly, Akalin et al. does not provide any suggestion or motivation of combining their teachings with the teachings of Lenschow, D.J. et al., Goosen et al. or Soon-Shiong P. et al. to arrive at the claimed method; nor is any reasonable expectation of success of the combination of these references provided.

Linsley, et al. provide the DNA sequence encoding the amino acid sequence corresponding to the CTLA4Ig receptor protein and identify

B7 antigen as a natural ligand for the CTLA4Ig receptor. Linsley et al. discuss a method of treating immune system diseases mediated by T cell interactions with B7 positive cells by administering a ligand reactive with B7 antigen to regulate T cell interactions with B7 positive cells, wherein the ligand may be CTLA4Ig fusion protein, the CD28Ig/CTLA4Ig fusion protein hybrid or a monoclonal antibody reactive with B7 antigen. (see page 4, lines 43-46) Linsley, et al. provide a method for blocking B7 interaction so as to regulate the immune response by contacting lymphocytes with a CTLA4Ig-binding molecule and an IL4-binding molecule. (see page 4, lines 50-52) At page 4, lines 55-57, Linsley et al. disclose a method for inhibiting tissue transplant rejection by a subject comprising administering to the subject a CTLA4Ig-binding molecule and an IL4-binding molecule. As stated on page 12, lines 37-39, Linsley et al. overcome problems associated with therapies directed to preventing the rejection of tissue or organ transplants by affecting only immunological responses mediated by B7 interactions. Therefore, Linsley et al. do not suggest combination with either when combined with Lenschow, et al. or Goosen et al. and even when Linsley et al. is combine with these references, the combination of references does not motivate one of skill to arrive at the claimed method, as discussed above, since neither Lenschow, et al., Goosen et al., or Linsley et al. suggest treatment which combines microencapsulation with administration of a drug such as CTLA4Ig.

Padrid P.A. et al., disclose that in an animal model of asthma, CTLA4Ig treatment can promote immune deviation (with a predominantly Th2-type pattern manipulated toward a Th1-type pattern) instead of a more global inhibition of T-cell effector

function. (see Padrid, page 461, column 2, second paragraph). After primary immunization with antigen, CTLA4Ig treatment resulted in statistically significant increased INF-γ production. However, the connection, if any, between the asthma model (asthma is a disease in which the patient has been previously sensitized prior to natural re-exposure to the antigen(s) that cause clinical symptoms), as stated in Padrid, page 461, column 1, second paragraph) and transplantation is unclear. Padrid et al. do not address any method(s) of inhibiting viable cells transplanted into a subject from being destroyed by the subject's immune system, as claimed, which comprises (a) containing the viable cells, or tissue comprising the viable cells, prior to transplantation within a device comprising a semipermeable membrane; **and** b) treating the subject with a substance which inhibits an immune-system costimulation event in an amount effective to inhibit the subject's immune system from responding to said contained cells or tissue. Since no connection of the asthma model to transplant rejection is established by Padrid et al. or any of the other cited references, the combination of Padrid et al. with any of the other cited references does not bolster or negate any of the other cited disclosures. Accordingly, Padrid et al. is improperly cited and should be removed as a citation against the subject application.

Finally, Steurer, W. et al. tests the hypothesis that blockade of B7-triggered CD28/CTLA4 costimulation by B7+ donor cells precludes allograft rejection without application of systemic immunosuppression and discloses that **ex vivo** coating of islet cell allografts (same species) with murine CTLA4Ig prior to transplantation promotes graft tolerance. (Emphasis added) Steurer,

W. et al. disclose at page 1173 that pretreatment of islet grafts with (NL)mCTLA4/Fc does not eliminate cellular responses to the allograft: the prominent mononuclear cell response tends to encircle, but not aggressively infiltrate the islet tissue, as is typical in rejection. Therefore, Steurer et al. do not suggest: 1) containing the viable cells, or tissue [islet cell allografts] comprising the viable cells, prior to transplantation **within a device comprising a semipermeable membrane**; and 2) treating **the subject** [mice] with a substance which inhibits an immune-system costimulation event in an amount effective to inhibit the subject's immune system from responding to said contained cells or tissue, as recited in claim 1. Coating ex vivo with CTLA4/Fc by Steurer, et al. does **not** provide any motivation to either microencapsulate prior to transplantation or to treat the subject with an inhibitory substance. Accordingly, Steurer et al. do not suggest a combination with Lenschow, et al., Goosen et al. or any of the other cited references to arrive at the claimed method. Therefore the combination of Steurer et al. with any or all of the other cited references does not render obvious the claimed method of inhibiting viable cells transplanted into a subject from being destroyed by the subject's immune system.

Applicants also respectfully direct the Examiner's attention to In re Rouffet, 47 USPQ2d 1453, 1457-1458 (Fed. Cir. 1998) which states:

> "To prevent the use of hindsight, this court requires the examiner to show a **motivation to combine the references** that create the obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted

> with the same problems as the inventor and with no knowledge of the claimed invention, **would select elements from the cited prior art for combination** in the manner claimed." (Emphasis added)

The Court further states that "the Board did not rely upon any of the three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. Rather, it relied upon the high level of skill in the art to provide the necessary motivation. The Board did **not** explain **what specific understanding or technological principle** within the knowledge of one of ordinary skill in the art would have **suggested the combination**." In re Rouffet, 47 USPQ2d 1453, 1458. (Applicants' emphasis) Therefore, a high level of skill in the art, without more, cannot supply the required motivation to combine references, and does **not** overcome absence of any actual suggestion to combine.

The Examiner has not explained at page 6 of the December 8, 1999 Office Action what knowledge would suggest the combination of references or provide the motivation to combine microencapsulation with CTLA4Ig treatment. The statement by the Examiner at page 2, second paragraph: "Prevention of graft rejection, but by a different mechanism, thus by logical reasoning, would increase the chance of preventing graft rejection by the immune system," does not appear to be supported by the combination of teachings of the cited art or by some specific understanding or technological principle within the knowledge of one of ordinary skill in the art.

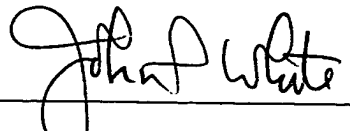
Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 2, 4-7, 9-17, 20-23, and 43-47 under 35 U.S.C. § 103(a).

In summary, in view of the amendments and remarks made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the grounds of rejection in the December 8, 1999 Office Action and earnestly solicit allowance of the claims now pending in the subject application, namely claims 1, 2, 4-7, 9-17, 20-23, and 43-47, as amended.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $55.00 for a one-month extension of time, is deemed necessary in connection with this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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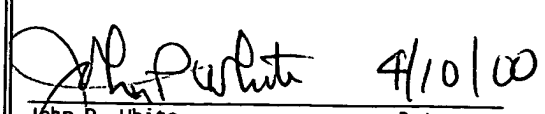
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



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